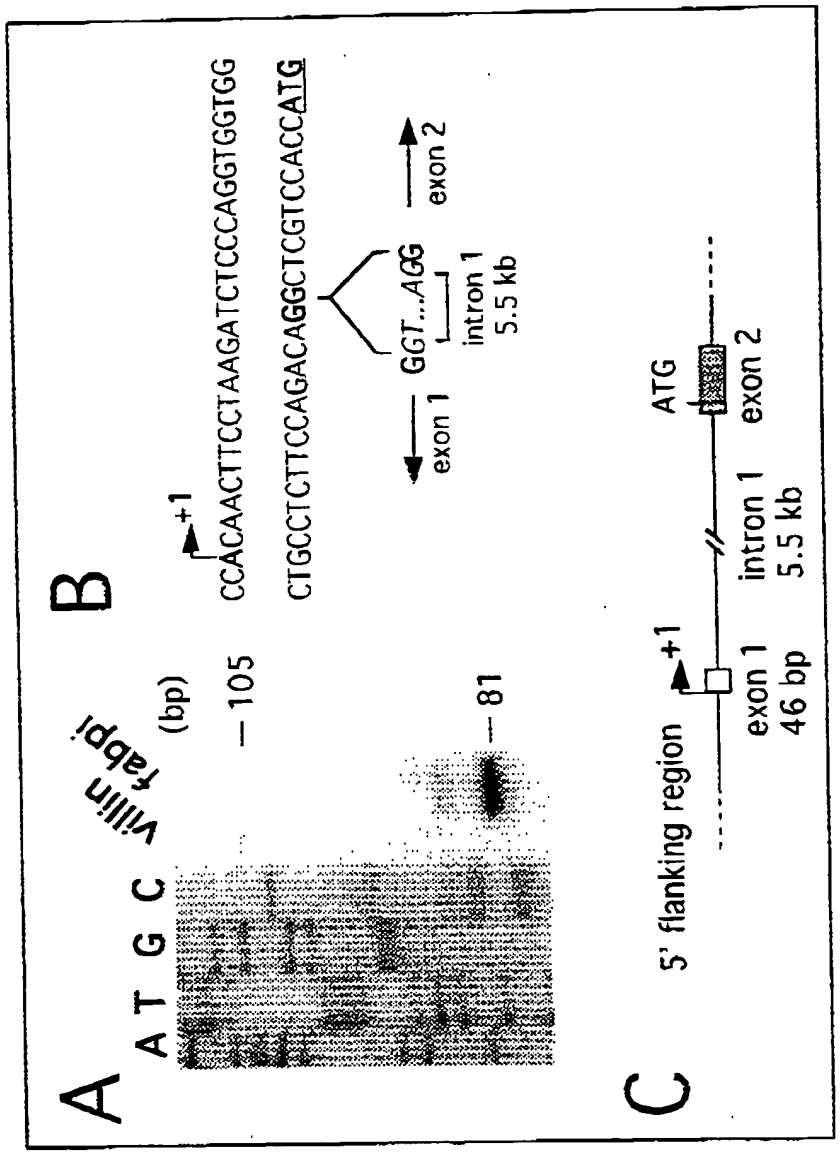
A
A T G C
Villin fabpi
(bp)
— 105
— 81
B
+1
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CTGCCTCTTCCAGACAGGCTCGTCCACCATG
GGT...AGG
exon 1
intron 1
5.5 kb
exon 2
C
5' flanking region
+1
ATG
exon 1
46 bp
intron 1
5.5 kb
exon 2

Figure 1

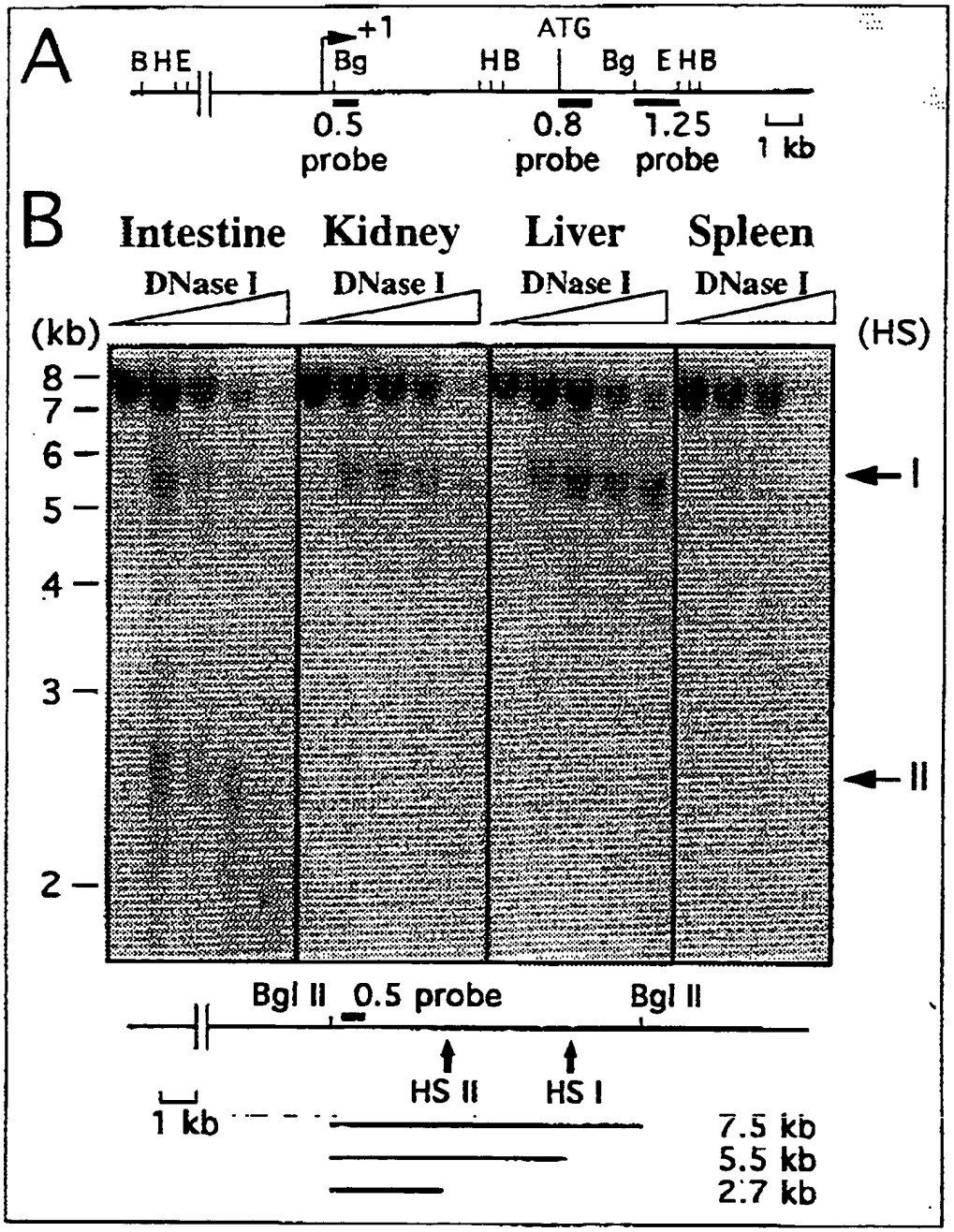
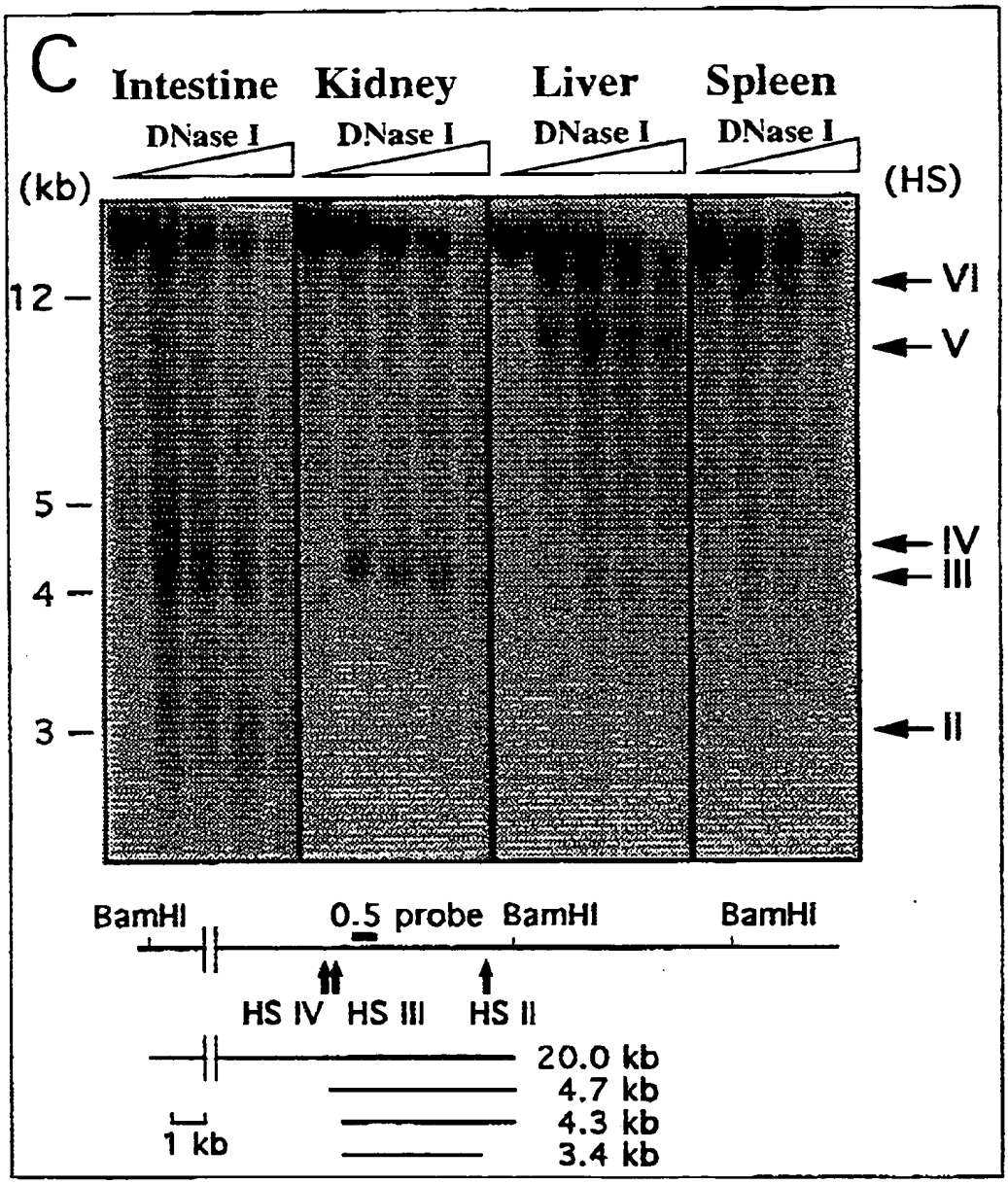

A
BHE
+1
Bg
ATG
HB
Bg
EHB
0.5 probe
0.8 probe
1.25 probe
1 kb
B
Intestine
Kidney
Liver
Spleen
DNase I
DNase I
DNase I
DNase I
(kb)
(HS)
8
7
6
5
4
3
2
I
II
Bgl II
0.5 probe
Bgl II
HS II
HS I
1 kb
7.5 kb
5.5 kb
2.7 kb

Figure 2 (a)


C
Intestine
Kidney
Liver
Spleen
DNase I
DNase I
DNase I
DNase I
(kb)
(HS)
12
5
4
3
VI
V
IV
III
II
BamHI
0.5 probe
BamHI
BamHI
HS IV
HS III
HS II
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4.7 kb
4.3 kb
3.4 kb
1 kb

Figure 2 (b)

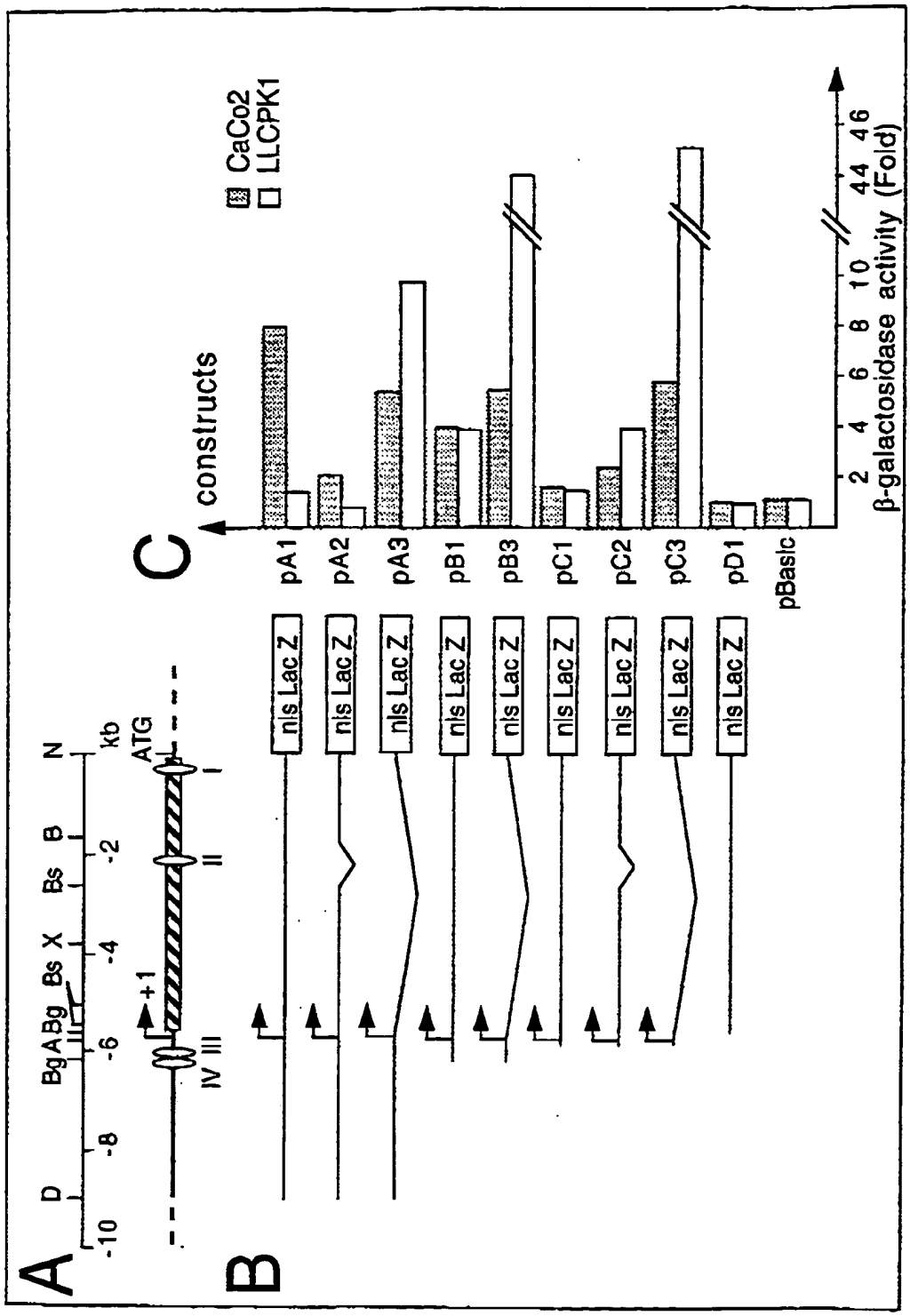
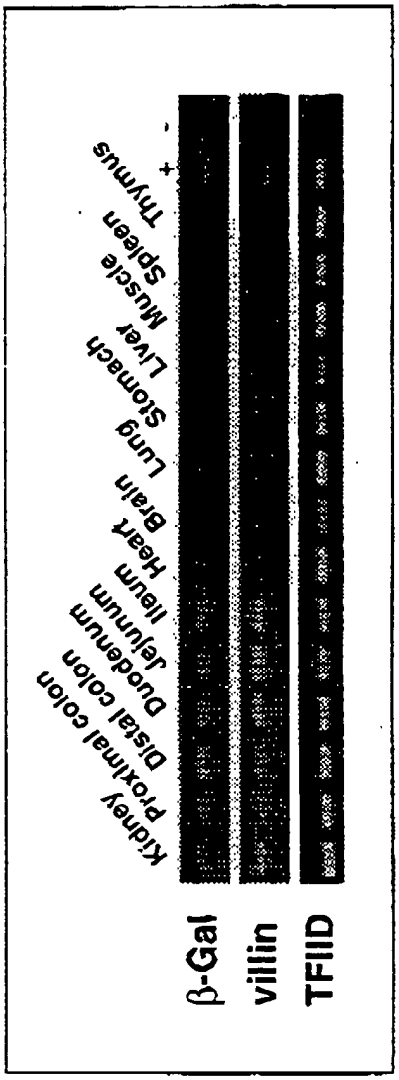

A
D
Bg A Bg Bs X Bs B N
kb
-10 -8 -6 -4 -2
ATG
+1
I
II
III
IV
B
nls Lac Z
C
constructs
CaCo2
LLCPK1
pA1
pA2
pA3
pB1
pB3
pC1
pC2
pC3
pD1
pBasic
2 4 6 8 10 44 46
β-galactosidase activity (Fold)

Figure 3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villin
TFIID
Kidney
Proximal colon
Distal colon
Duodenum
Jejunum
Ileum
Heart
Brain
Lung
Stomach
Liver
Muscle
Spleen
Thymus
+
-

Figure 4

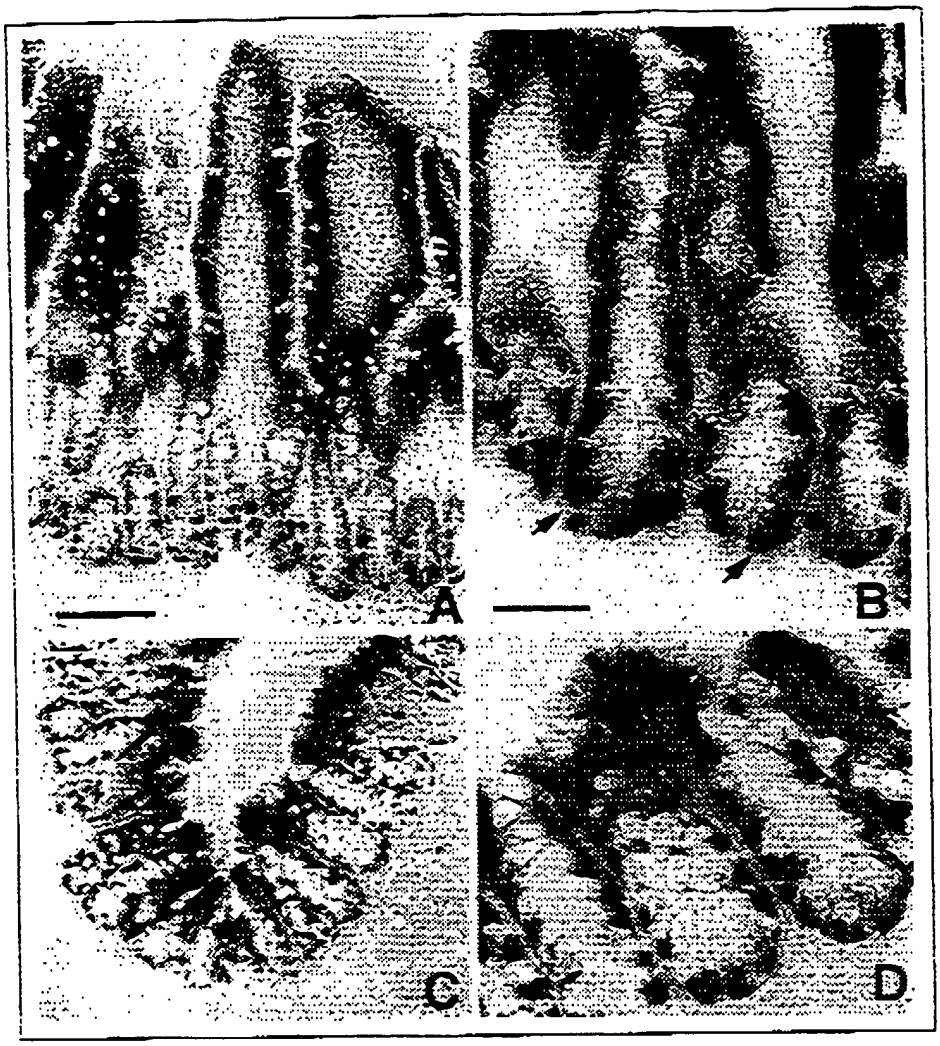

Figure 5

Genomic sequence of the mouse villin gene regulat ry s quences

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GTCCATTCAG GATGGACCAT CCTATAAGAT GATTCTCTTG ACCCAGGTAA GCTAATGTCA 420
TGGGGAAAGG GGATGGGACT GTCCTAGATT AAAAAGTGCT GAGGCGATGC CTATTCTCAA 480
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+1 exon 1

(transcription start site)

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exon 2

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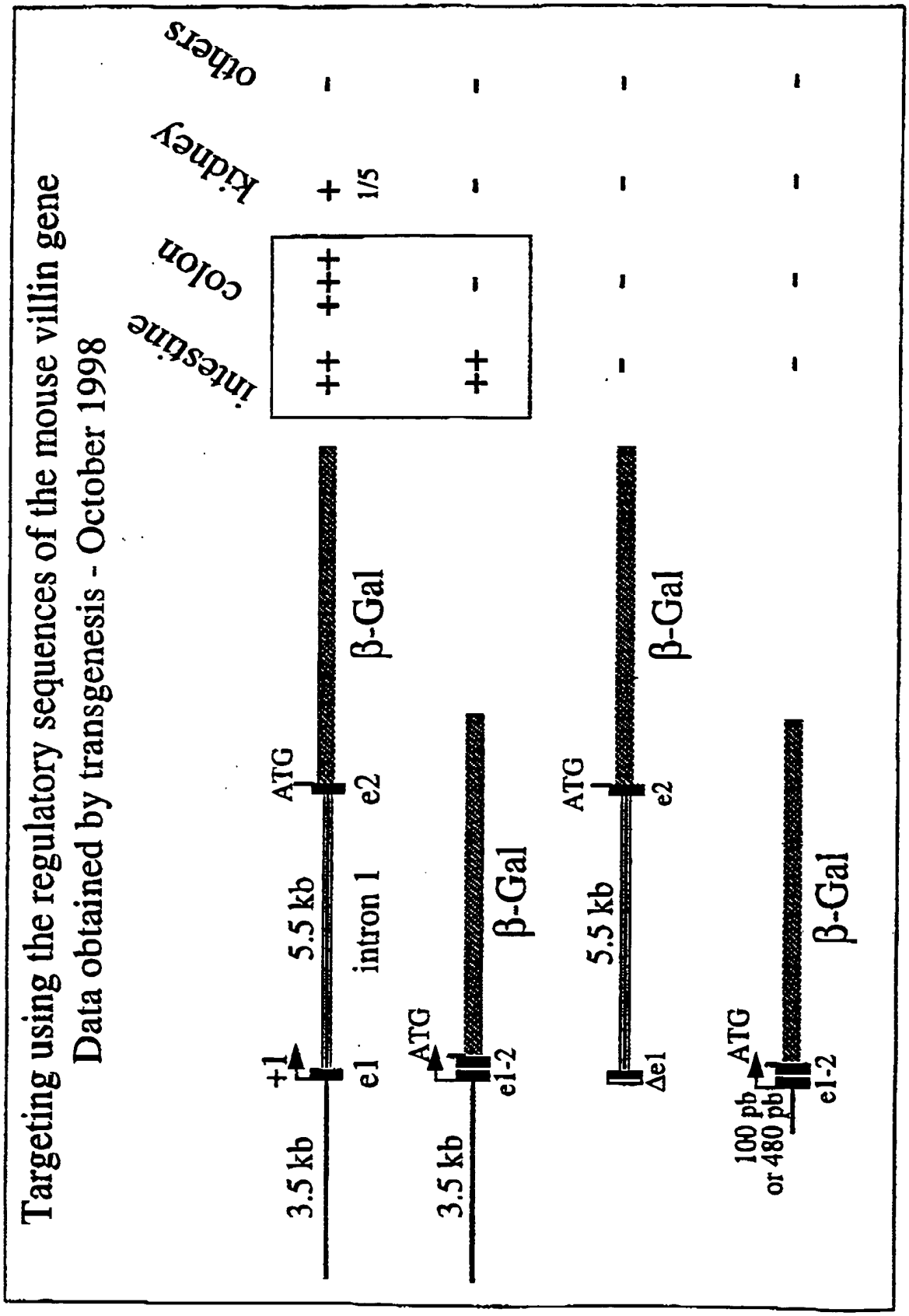
Targeting using the regulatory sequences of the mouse villin gene
Data obtained by transgenesis - October 1998
intestine
colon
kidney
others
++
+++
+
-
1/5
3.5 kb
+1
e1
5.5 kb
intron 1
ATG
e2
β-Gal
3.5 kb
ATG
e1-2
β-Gal
5.5 kb
ATG
e2
β-Gal
Δe1
100 pb
or 480 pb
ATG
e1-2
β-Gal

Figure 7

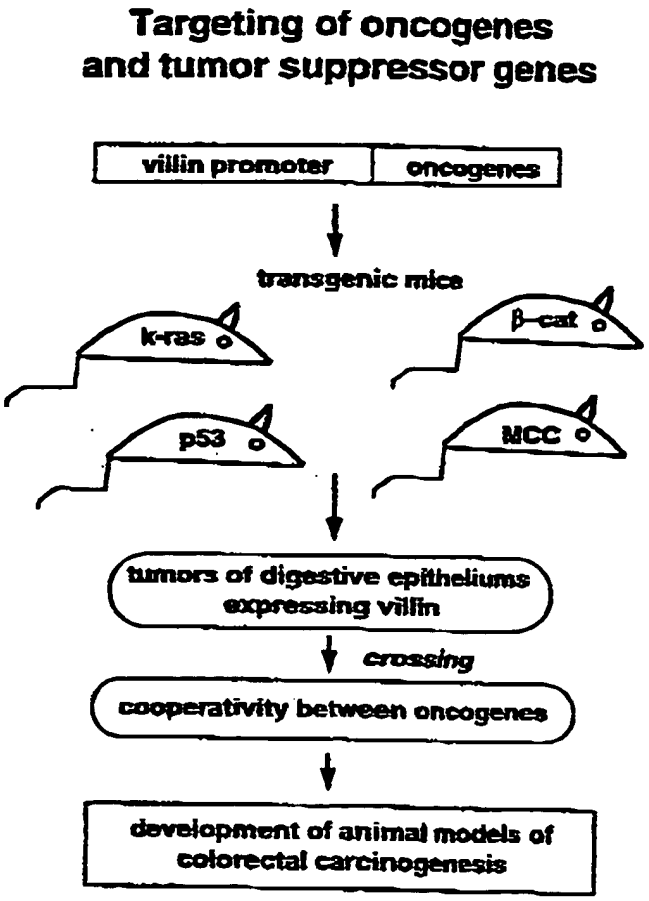
Targeting of oncogenes
and tumor suppressor genes
villin promoter
oncogenes
transgenic mice
k-ras
β-cat
p53
MCC
tumors of digestive epitheliums
expressing villin
crossing
cooperativity between oncogenes
development of animal models of
colorectal carcinogenesis

FIGURE 8A

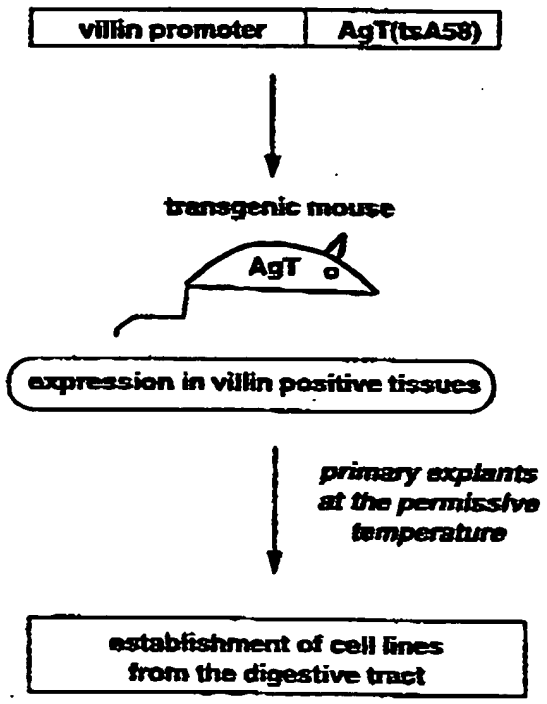
Targeting of immortalizing gene
villin promoter
AgT(tsA58)
transgenic mouse
AgT
expression in villin positive tissues
primary explants
at the permissive
temperature
establishment of cell lines
from the digestive tract

FIGURE 8B

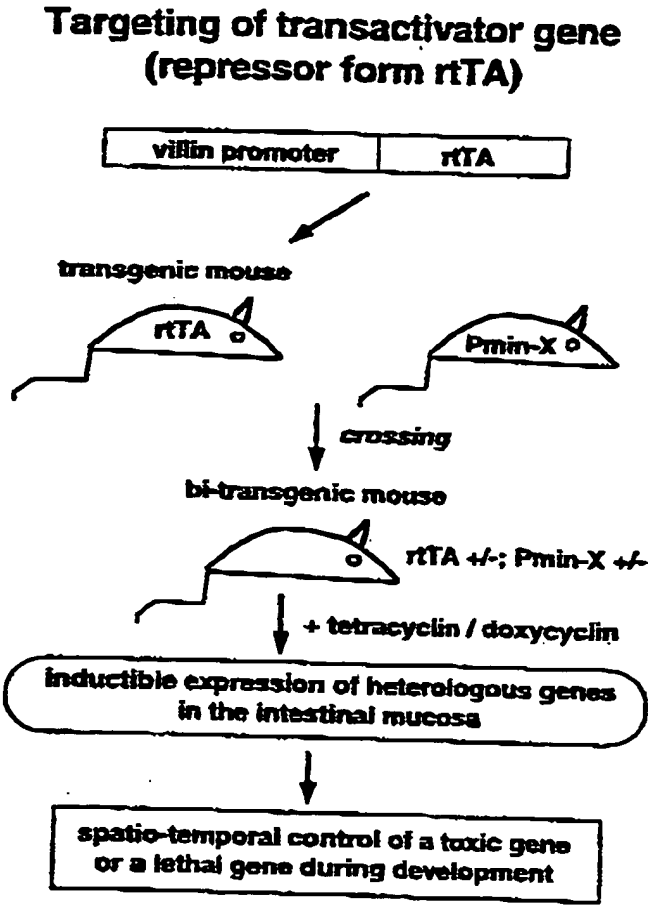
Targeting of transactivator gene
(repressor form rtTA)
villin promoter
rtTA
transgenic mouse
rtTA
Pmin-X
crossing
bi-transgenic mouse
rtTA +/-; Pmin-X +/-
+ tetracyclin / doxycyclin
inductible expression of heterologous genes
in the intestinal mucosa
spatio-temporal control of a toxic gene
or a lethal gene during development

FIGURE 8C